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Stereocontrolled Synthesis of 1,2- and 1,3-Diamine Building Blocks from Aziridine Aldehyde Dimers

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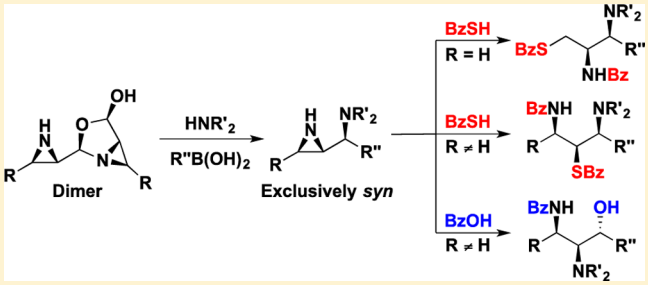
Supporting Information

ABSTRACT: Vicinal aziridine-containing diamines have been obtained with high *syn*-stereoselectivity from readily available aziridine aldehyde dimers in the Petasis borono-Mannich reaction. Subsequent solvent- and/or nucleophile-dependent ring-opening of the aziridine ring yields functionalized 1,2- and 1,3-diamines with high regioselectivity. The ring opening is also influenced by the substitution at the C3 position of the aziridine. A mechanistic rationale for the highly *syn*-selective three-component reaction is proposed.



INTRODUCTION

Chiral nitrogen-containing molecules, particularly vicinal diamines, have received a substantial amount of attention in chemical synthesis.[1−3] They have been used as ligands[1,4] and as precursors to ligands, such as N-heterocyclic carbenes,[5] which have in turn found utility in a myriad of catalytic enantio- and diastereoselective bond-forming reactions. In addition, natural products containing piperazine substructures[6] and antibacterials such as ficellomycin[7,8] and mitomycins[9,10] all contain diamine cores. Previously reported synthetic routes to vicinal diamines are based on the reduction of diazide[11,12] and dinitro[13] species, substitution of diols,[14,15] and ring-opening of activated aziridines,[16−18] among others. The synthetic diversity and broad mode of application of chiral diamines prompted us to explore the synthesis of aziridine-containing diamines using aziridine aldehyde dimers as building blocks. The templates we describe should enable facile access to a wide range of functionalized molecules depending on the regioselectivity of aziridine ring-opening.

Motivated by the utility of aziridine aldehyde dimers in multicomponent reactions, we focused our attention on the Petasis borono-Mannich (PBM) process,[19] which is known to produce *anti* amino alcohols from α-hydroxyaldehydes, amines, and boronic acids.[20,21] The established *anti* selectivity relies on the presence of the α-hydroxyl moiety in aldehyde **1** (Figure 1).[22−24] The boronic acid "ate" complex **3** is believed to be formed subsequent to condensation between an aldehyde and an amine. The reduction of 1,3-allylic strain biases the boronate complex to attack the *re* face of the iminium ion, preferentially generating *anti* amino alcohols such as **4**.[25,26]

The stereoselectivity of the PBM reaction with α-hydroxy aldehydes is reliable but limits the use of this method to the generation of products with *anti* stereochemistry. In a recent report, a chiral catalyst in a mismatched pairing with the chiral α-hydroxy aldehyde furnished *syn* amino alcohols.[27] As part of a program aimed at the chemistry of unprotected amino aldehydes, we asked a question about the effect a nucleophilic α-nitrogen has on the stereoselectivity of iminium attack by a boronate nucleophile. Because of the inherent instability of chiral aldehydes equipped with the nucleophilic α-nitrogen,[28] there has been little opportunity to examine the effect of this moiety on the PBM process. Aziridine aldehyde dimers have been previously showcased in a variety of solvent-dependent transformations.[29] Our studies have shown that the dimeric nature of aziridine aldehydes plays a significant chemo- and stereodifferentiating role. Herein, we report a highly *syn*-selective PBM reaction employing amphoteric aziridine aldehydes to generate aziridine-containing vicinal diamines. Aziridine ring-opening of our products exhibits anchimeric assistance en route to functionalized 1,2- and 1,3-diamines. We also propose an experimentally derived model that explains the unusual *syn*-selectivity observed in this chemistry.

RESULTS AND DISCUSSION

Using excess morpholine and styrenyl boronic acid as model PBM reaction components, a solvent screen was performed with a phenylethyl-substituted dimer (Table 1). Using 1,1,1-trifluoroethanol (TFE) as solvent allowed for rapid conversion of the starting material to the dimer−morpholine adduct **7a** but slow subsequent conversion to diamine **8a** (entry 1). Fortunately, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) allowed for the conversion to diamine **8a** to dominate (entry 2). The use of methylene chloride, water, or ethanol as cosolvents with HFIP either completely stalled the reaction at the dimer−morpholine adduct stage or slowed the conversion to the diamine (entries 3−5).

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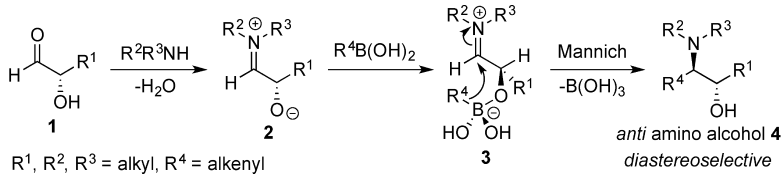
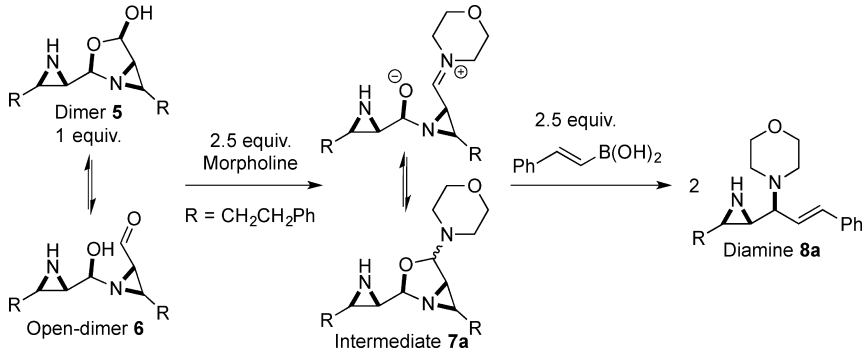


Figure 1. Petasis borono-Mannich reaction with α-hydroxy aldehydes.

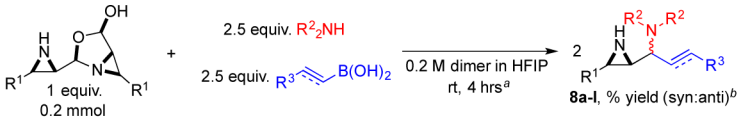
Table 1. Solvent-Dependent Conversion to Diamine Product 8a

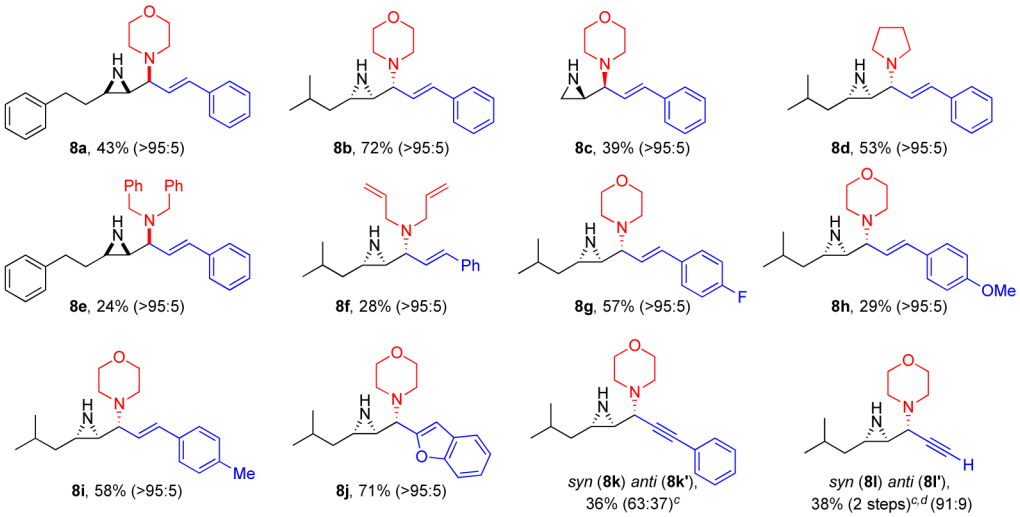


		relative LC/MS peak integrations[a] after 1 h		
entry	solvent[b]	dimer **5**	intermediate **7a**	diamine **8a**
1	TFE	1	5	0.5
2	HFIP	1	2	3
3	1:1 HFIP/DCM	1	1	1
4	5:1 HFIP/H_2O	1	0.5	0
5	1:1 HFIP/EtOH	1	20	0

[a]The LC/MS trace peaks corresponding to each of the desired [M + 1] ions were integrated to approximate the relative degree of conversion in each case. [b]0.2 M of dimer. TFE = 2,2,2-trifluoroethanol; HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol; DCM = dichloromethane.

Table 2. Substrate Scope of the Petasis Borono–Mannich Reaction





[a]See the Experimental Section for more details. [b]Isolated yields after column chromatography. Yields are calculated assuming one aziridine aldehyde dimer produces two diamines. *syn* to *anti* ratio determined by crude NMR. [c]Prepared using pinacol boronic esters; combined yields. [d]A TMS ethynyl boronic ester was prepared and deprotected according to literature procedures.[30,31]

Successful synthesis of diamine **8a** prompted us to evaluate the scope of the PBM reaction (Table 2). Substituted and unsubstituted aziridine aldehydes prepared by literature procedures[29] were tested with the model reactants, and each

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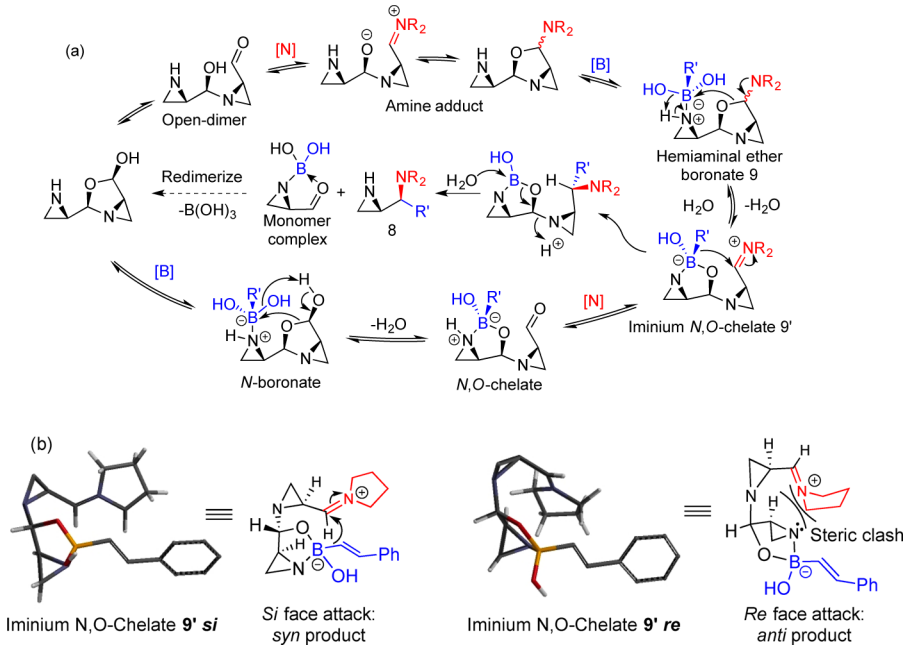
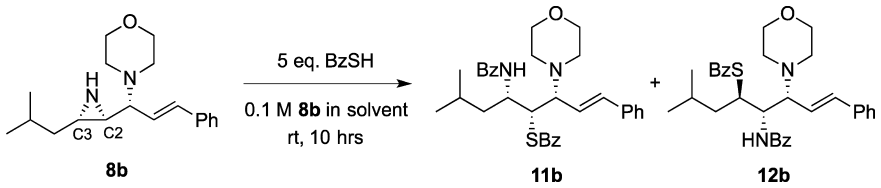


Figure 2. Proposed mechanism. (a) Pathways to key intermediate **9′** and the dissociation of the complex to furnish product and aziridine aldehyde monomer. (b) 3D conformational rationale for high *syn* selectivity of iminium *N,O*-chelate **9′**. *Nonminimized* structures represent the two rotamers required to align the *si* and *re* faces of the iminium to allow for alkenyl migration. Selected protons are omitted for clarity.[36].

Table 3. Solvent-Dependent Aziridine Ring-Opening of 8b



8b **11b** **12b**

entry	solvent	ratio[a] (**11b**:**12b**)
1	$CHCl_3$	>95:5
2	MeOH	>95:5
3	MeCN	65:35
4	TFE	58:42
5	9:1 TFE/H_2O	57:43
6	8:2 HFIP/H_2O	35:65

[a]Determined by ^{1}H NMR of crude product after workup. Bz = benzoyl.

exhibited full conversion of the limiting reagent to diamines **8a–c** with high diastereoselectivity, as determined by crude ^{1}H NMR (only one diastereomer was detected). The reaction of various secondary amines **8d–f**, as well as heteroaromatic and *para*-substituted styrenyl boronic acids **8g–j** proceeded with full conversion, high diastereoselectivity, and varying yields. Alkynyl pinacol boronic esters were also utilized to generate diamines **8k–l**[30,31] but with an observable loss of selectivity.[32] Aryl boronic acids were unreactive,[33] yielding only the dimer–amine adducts such as **7**, while the use of primary amines, such as benzylamines and anilines led to intractable mixtures of products.

The two diastereomers isolated from the less selective ethynyl pinacol boronic ester cases (**8k–l**) were chromatographically separable and produced very distinct chemical shifts and coupling constants between the protons attached to the two contiguous amine stereocenters (see the Supporting Information). The assignment of *syn* and *anti* stereochemistry was not apparent, however, until the structure of **8c** was confirmed by single-crystal X-ray crystallography (see the Supporting Information). Interestingly, the crystal structure revealed that the PBM reaction using aziridine aldehyde dimers yields *syn* diamines in contrast to the more common *anti* products. The diagnostic ^{1}H NMR chemical shifts and coupling constants of **8c** were used in order to assign the correct stereochemistry for all other substrates.

The highly stereodifferentiating nature of the aziridine aldehyde open-dimer state is the likely determinant of *syn* selectivity. Two paths can be followed to arrive at the pivotal boronates **9** and **9′** (Figure 2a). The key intermediate is likely to exist as *N,O*-chelate **9′** that may be produced from the corresponding hemiaminal ether **9**.[34] A mechanistic rationale involving iminium *N,O*-chelate **9′** is consistent with the preferred alkenyl group migration onto the *si* face of the iminium ion. The alternative attack onto the *re* face involves unfavorable steric interactions in the proposed pretransition state assembly (Figure 2b).[35] Alkenyl migration onto the *si* face and dissociation of the complex would furnish *syn* diamine **8** as

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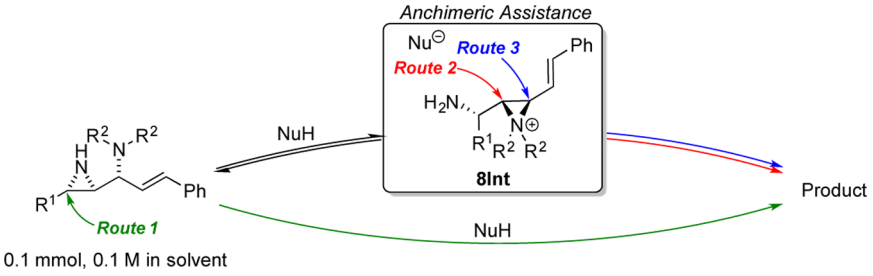
Table 4. Aziridine Ring-Opening Scope



Entry	Substrate	Nucleophile (equiv.)	Route(s) of Attack[a] Selectivity[b] % Yield	Product
1	**8a**	BzSH[c] (5)	**2** vs. **1** >95:5 52%	**11a**
2	**8b**	BzSH (5)	**2** vs. **1** >95:5 61%	**11b**
3	**8c**	BzSH (5)	**1** vs.**2** 85:15 48%[c]	**12c**
4	**8d**	BzSH (5)	**2** vs. **1** >95:5 68%	**11d**
5	**8f**	BzSH (5)	**2** vs. **1** 85:15 77%	**11f**
6	**8a**	*p*-NO_2BzOH[d] (1.2)	**3** vs. **1**/**2** 80:20 37%	**13a**
7	**8b**	*p*-NO_2BzOH (1.2)	**3** vs. **1**/**2** 80:20 50%	**13b**
8	**8d**	*p*-NO_2BzOH (1.2)	**3** vs. **1**/**2** >95:5 80%	**13d**

[a]"Routes of attack" defined by major route vs minor route(s). [b]Selectivity of the major and minor routes by crude ^{1}H NMR. [c]Reactions with BzSH run in chloroform at room temperature for 10 h. [d]Reactions with *p*-NO_2BzOH run with 10 mol % of triethylamine in DMF, 65 °C for 24 h. Bz = benzoyl.

well as boron-chelated aziridine aldehyde monomer. The monomer is recycled into the reaction via redimerization.

To evaluate the utility of our aziridine-containing diamines, ring-opening using thiobenzoic acid was examined. When **8b** was reacted with 1 equiv of thiobenzoic acid in chloroform, mono- and bis-benzoylated products were observed due to sulfur-to-nitrogen benzoyl transfer. An excess of thiobenzoic acid was subsequently used in our studies. Surprisingly, a single regioisomer **11b** was generated in chloroform, which was confirmed by 2D ^{1}H NMR (Table 3, entry 1). The C2 selectivity in methanol still remained very high, aside from other methanolysis byproducts, while in acetonitrile the C2 selectivity was diminished to a 65:35 ratio of **11b** to **12b** (entries 2 and 3, respectively). An increase in solvent polarity led to an increased propensity for C3 attack to a point where the C3-regioisomer was the major product in an 8:2 HFIP/water mixture (Table 3, entry 6). To examine the possibility of interconversion between **11b** and **12b**, they were each purified and stirred with thiobenzoic acid in 8:2 HFIP/water and chloroform, respectively. No interconversion was observed after 16 h.

Other chiral diamine substrates were ring-opened in chloroform (Table 4, entries 1–4). Similar C2 regioselectivity was observed with C3-substituted precursors, giving rise to products **11a**, **11d**, and **11f** (route 2). On the other hand, C3-unsubstituted diamine **8c** yielded the C3 regioisomer **12c** as the dominant product in chloroform, whereby attack at the least hindered center became a competing process (route 1). The newly formed C–S bond as well as the alkene functionality of **11a** and **11b** were successfully reduced with Raney nickel to yield long-chain chiral 1,3-diamines **14a** and **14b** in good yields over two steps (Figure 3).

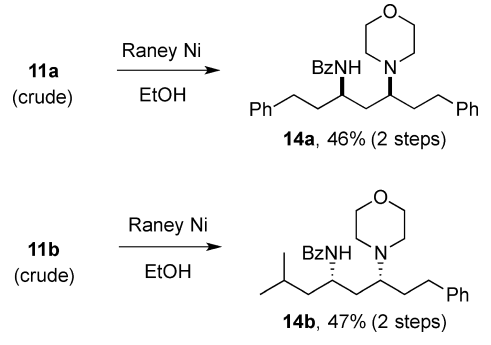


Figure 3. Raney nickel reduction of ring-opened substrates.

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We propose that anchimeric assistance of the tertiary amine contributes to the high C2 selectivity observed in our study. Accordingly, a diminished selectivity is observed in polar protic solvents, which mask the nucleophilicity of the amine lone pair. An unambiguous proof of such a mechanism would be to determine the absolute stereochemistry of the products whereby a net double inversion mechanism would result in retention of configuration at the C2 center. Extensive efforts were taken to produce X-ray quality crystals of thiobenzoic acid ring-opened products **11** and its derivatives, but thus far they have been unsuccessful. This prompted us to look for alternative nucleophiles.

Substrates **8a**, **8b**, and **8d** were reacted with *p*-nitrobenzoic acid, which required elevated temperatures and catalytic base to achieve full conversion to products **13** (Table 4, entries 6−8). Gratifyingly, one major regioisomer was produced in each case with **13d** showing the highest selectivity. Diaminohydroxyalkene **13d** crystallized readily and furnished X-ray quality crystals (see the Supporting Information). The X-ray crystal structure further solidified our proposal of the neighboring group effect (route 3). The oxygen nucleophile attacked the carbon adjacent to the alkene, resulting in a net 1,2-shift of the tertiary amine with concomitant aziridine ring-opening, and subsequent *O*- to *N*-benzoyl transfer. The relative stereochemistry of the ring-opened products supports a neighboring-group assisted process. An aziridinium ion **8Int** is proposed to be the key intermediate prior to nucleophilic attack. We note that route 3 is not observed in thiobenzoic acid ring-opening, but all evidence allows us to confidently assign the stereochemistry of the thiobenzoic acid ring-opened products. Other nucleophiles such as thiophenol and azide were found to be unreactive.

CONCLUSIONS

To conclude, we report the first exclusively *syn*-selective Petasis borono-Mannich reaction that generates aziridine-containing vicinal diamine products. The chiral building blocks described in this paper can be easily synthesized from readily available starting materials with high diastereoselectivity. The aziridine-containing diamines exhibit significant solvent and nucleophile dependent regioselectivity of ring-opening to produce 1,2- or 1,3-diamines containing three contiguous stereocenters. A defining factor controlling the observed regioselectivity lies in the presence of the neighboring tertiary amine, which participates in the reaction. The products have the potential to be used as chiral diamine building blocks for organic synthesis, as well as chiral multidentate ligands for asymmetric catalysis.

EXPERIMENTAL SECTION

General Procedure for the Three-Component PBM Reaction with Aziridine Aldehydes. Aziridine aldehyde dimers were prepared following literature procedures.[29]

Aziridine aldehyde (0.1 mmol) and boronic acid (0.25 mmol) were weighed and combined into a 2 dram screw-cap vial. HFIP (0.5 mL) was added, and the heterogeneous mixture was cooled to 0 °C. The secondary amine (0.25 mmol) was added dropwise via syringe along the side of the wall and stirred on ice for 10 min at room temperature for a total of 4 h. Consumption of starting material and intermediate aminal was monitored by LC/MS and TLC, and the yellow/orange reaction was concentrated in vacuo, dissolved in ethyl acetate, and washed with 20% NaOH to remove excess boronic acid. The organic layer was washed with brine, dried over sodium sulfate, and concentrated to yield a dark yellow to orange gel, which was purified by silica gel column chromatography. The eluent system generally was a gradient from ethyl acetate to 10% methanol in ethyl acetate. The high polarity of the eluent inevitably coelutes an unidentified yellow impurity to furnish a sticky pale yellow solid in most cases but does not compromise purity.

*4-((S,E)-1-((2S,3R)-3-Phenethylaziridin-2-yl)-3-phenylallyl)-morpholine (**8a**).* Scale: 1.0 g dimer (2.85 mmol). Yield: 1.105 g, 56%, pale yellow solid. R_f (1:4 MeOH/EtOAc): 0.30. Mp: 93−95 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.45−7.08 (m, 10H), 6.46 (d, J = 15.9 Hz, 1H), 6.17 (dd, J = 15.9, 8.8 Hz, 1H), 3.74 (t, J = 4.7 Hz, 4H), 2.76−2.59 (m, 6H), 2.33 (dd, J = 8.6, 7.6 Hz, 1H), 1.91 (dd, J = 7.6, 2.4 Hz, 1H), 1.81−1.66 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.5, 136.5, 133.5, 128.7, 128.4, 128.4, 128.0, 127.3, 126.5, 126.0, 73.5, 67.1, 51.8, 39.8, 35.6, 34.7, 33.8. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3273, 3025, 2959, 2921, 2856, 1601, 1496, 1448, 1269, 1117. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{23}H_{29}N_2O$ 349.2280, found 349.2286.

*4-((R,E)-1-((2R,3S)-3-Isobutylaziridin-2-yl)-3-phenylallyl)-morpholine (**8b**).* Scale: 0.075 g dimer (0.295 mmol). Yield: 0.127 g, 72%, pale yellow solid. R_f (1:9 MeOH/EtOAc): 0.20. Mp: 101−104 °C. ^{1}H NMR (399 MHz, $CDCl_3$) δ: 7.45−7.19 (m, 5H), 6.48 (d, J = 15.9 Hz, 1H), 6.19 (dd, J = 15.9, 8.9 Hz, 1H), 3.74 (t, J = 4.7 Hz, 4H), 2.78−2.58 (m, 4H), 2.31 (t, J = 8.2 Hz, 1H), 1.86 (dd, J = 7.7, 3.1 Hz, 1H), 1.76−1.62 (m, 2H), 1.34 (app. dt, J = 13.3, 6.6 Hz, 1H), 1.24 (app. dt, J = 13.3, 6.6 Hz, 1H), 0.89 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.7, 133.3, 128.8, 128.7, 127.9, 126.5, 73.8, 67.2, 52.0, 43.4, 39.7, 33.9, 27.6, 22.7, 22.7. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3273, 2955, 2898, 1601, 1496, 1450, 1282, 1269, 1118, 1071, 1003, 970. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{19}H_{29}N_2O$ 301.2280, found 301.2285.

*4-((S,E)-1-((S)-Aziridin-2-yl)-3-phenylallyl)morpholine (**8c**).* Scale: 0.039 g dimer (0.274 mmol). Yield: 0.053 g, 39%, pale yellow solid. Mp: 123−127 °C. Recrystallization by slow evaporation in a water/acetonitrile mixture to afford X-ray quality crystals. R_f (1:9 MeOH/EtOAc): 0.15. ^{1}H NMR (399 MHz, $CDCl_3$) δ: 7.44−7.19 (m, 4H), 6.48 (d, J = 15.9 Hz, 1H), 6.19 (dd, J = 15.9, 8.7 Hz, 1H), 3.75 (t, J = 4.5 Hz, 4H), 2.86−2.52 (m, 4H), 2.30 (dd, J = 8.6, 7.7 Hz, 1H), 2.18 (ddd, J = 7.6, 6.0, 3.5 Hz, 1H), 1.79 (d, J = 6.0 Hz, 1H), 1.40 (d, J = 3.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.6, 133.4, 128.7, 127.9, 127.6, 126.5, 73.8, 67.2, 52.0, 32.4, 22.64. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3290, 3056, 3024, 2993, 2959, 2916, 2854, 2817, 1601, 1496, 1451, 1269, 1117, 1069, 1009, 971. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{15}H_{21}N_2O$ 245.1654, found 245.1658.

*1-((R,E)-1-((2R,3S)-3-Isobutylaziridin-2-yl)-3-phenylallyl)-pyrrolidine (**8d**).* Scale: 0.051 g dimer (0.2 mmol). Yield: 0.0776 g, 68%, pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40−7.36 (m, 2H), 7.34−7.30 (m, 2H), 7.27−7.22 (m, 1H), 6.49 (d, J = 15.8 Hz, 1H), 6.31 (dd, J = 15.9, 9.0 Hz, 1H), 2.75 (tq, J = 7.4, 3.0 Hz, 4H), 2.36−2.28 (t, J = 8.5 Hz, 1H), 2.00 (dd, J = 7.8, 3.1 Hz, 1H), 1.87 −1.78 (m, 4H), 1.75−1.64 (m, 2H), 1.34 (dt, J = 13.2, 6.5 Hz, 1H), 1.24 (dt, J = 13.6, 6.7 Hz, 1H), 0.89 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 136.7, 132.2, 128.7, 128.6, 127.8, 126.5, 72.9, 52.5, 43.4, 40.8, 33.9, 27.6, 23.2, 22.7, 22.6. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3159, 2962, 2948, 2930, 2906, 2871, 2807, 2788, 1495, 1448, 1383, 1152, 967, 920. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{19}H_{29}N_2$ 285.2320, found 285.2325.

*(S,E)-N,N-Dibenzyl-1-((2S,3R)-3-phenethylaziridin-2-yl)-3-phenylprop-2-en-1-amine (**8e**).* Scale: 0.1 g dimer (0.285 mmol). Yield: 0.261 g, 24%, pale yellow gel. R_f (1:1 Hex/EtOAc): 0.70. ^{1}H NMR (399 MHz, $CDCl_3$) δ: 7.48−7.02 (m, 20H), 6.43 (d, J = 15.9 Hz, 1H), 6.24 (dd, J = 15.9, 8.3 Hz, 1H), 3.95 (d, J = 13.6 Hz, 2H), 3.56 (d, J = 13.7 Hz, 2H), 2.91 (t, J = 8.3 Hz, 1H), 2.81−2.57 (m, 2H), 2.04 (dd, J = 6.4, 2.2 Hz, 1H), 1.80−1.59 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.8, 140.1, 136.8, 134.7, 128.8, 128.8, 128.5, 128.5, 128.4, 128.0, 127.1, 126.6, 125.9, 125.2, 64.6, 54.4, 39.4, 35.8, 35.4, 33.8. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3286, 3104, 3083, 3060, 3025, 2923, 2839, 2806, 1602, 1496, 1489, 1448, 1373, 1120, 1073, 1028, 969. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{33}H_{35}N_2$ 459.2800, found 459.2795.

*(R,E)-N,N-Diallyl-1-((2R,3S)-3-isobutylaziridin-2-yl)-3-phenylprop-2-en-1-amine (**8f**).* Scale: 0.1 g dimer (0.39 mmol). Yield: 0.0485 g, 28%, yellow gel. R_f (1:9 MeOH/EtOAc): 0.64. ^{1}H NMR (300 MHz,

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$CDCl_3$) δ: 7.48−7.19 (m, 5H), 6.46 (d, J = 16.0 Hz, 1H), 6.18 (dd, J = 15.9, 8.4 Hz, 1H), 5.86 (dddd, J = 17.1, 10.1, 7.0, 5.6 Hz, 2H), 5.31−5.06 (m, 4H), 3.39 (ddt, J = 14.2, 5.7, 1.6 Hz, 2H), 3.20 (ddt, J = 14.2, 6.9, 1.2 Hz, 2H), 2.97 (app. t, J = 7.5 Hz, 1H) 1.88 (dd, J = 6.9, 3.1 Hz, 1H), 1.83−1.62 (m, 2H), 1.30 (t, J = 6.6 Hz, 2H), 0.91 (d, J = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.0, 136.5, 133.4, 128.7, 127.8, 127.1, 126.5, 117.3, 66.6, 53.5, 43.3, 39.6, 34.7, 27.5, 22.9, 22.7. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3283, 3078, 3021, 2955, 2955, 2876, 1641, 1599, 1495, 1467, 1449, 1418, 1385, 1368, 1261, 1100, 970, 918. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{31}N_2$ 311.2484, found 311.2487.

*4-((R,E)-3-(4-fluorophenyl)-1-((2R,3S)-3-isobutylaziridin-2-yl)-allyl)morpholine (**8g**).* Scale: 0.0508 g dimer (0.2 mmol). Yield: 0.073 g, 57%, pale yellow solid. R_f (1:9 MeOH/EtOAc): 0.14. ^{1}H NMR (399 MHz, $CDCl_3$) δ: 7.36−7.29 (m, 2H), 7.04−6.97 (m, 2H), 6.43 (d, J = 15.9 Hz, 1H), 6.09 (dd, J = 15.9, 8.9 Hz, 1H), 3.73 (t, J = 4.7 Hz, 4H), 2.74−2.58 (m, 4H), 2.29 (t, J = 8.3 Hz, 1H), 1.85 (dd, J = 7.7, 3.1 Hz, 1H), 1.74−1.60 (m, 2H), 1.37 (dt, J = 13.2, 6.5 Hz, 2H), 1.22 (dt, J = 13.6, 6.7 Hz, 1H), 0.89 (d, J = 6.7, 3H), 0.88 (d, J = 6.7, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.5 (d, $^1J_{CF}$ = 246.99), 132.9 (d, $^4J_{CF}$ = 3.56 Hz), 132.0, 128.0 (d, $^3J_{CF}$ = 8.41 Hz), 127.7, 115.7 (d, $^2J_{CF}$ = 21.92 Hz), 73.7, 67.2, 52.0, 43.4, 39.7, 34.0, 27.6, 22.7. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3270, 2923, 2916, 2868, 1602, 1509, 1505, 1453, 1269, 1228, 1158, 1118, 1002, 973, 879, 859. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{28}FN_2O$ 319.2186, found 319.2192.

*4-((R,E)-1-((2R,3S)-3-Isobutylaziridin-2-yl)-3-(4-methoxyphenyl)-allyl)morpholine (**8h**).* Scale: 0.051 g dimer (0.2 mmol). Yield: 0.038 g, 29%, yellow solid. R_f (1:9 MeOH/EtOAc): 0.32. ^{1}H NMR (399 MHz, $CDCl_3$) δ: 7.33−7.28 (m, 2H), 6.91−6.83 (m, 2H), 6.41 (d, J = 15.7 Hz, 1H), 6.03 (dd, J = 15.8, 8.9 Hz, 1H), 3.81 (s, 3H), 3.74 (t, J = 4.7 Hz, 4H), 2.73−2.60 (m, 4H), 2.29 (t, J = 8.2 Hz, 1H), 1.86 (dd, J = 7.7, 3.1 Hz, 1H), 1.79−1.55 (m, 2H), 1.35 (dt, J = 13.3, 6.5 Hz, 1H), 1.24 (dt, J = 13.3, 6.5 Hz, 1H), 0.89 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.5, 132.8, 129.5, 127.7, 125.6, 114.2, 73.9, 67.2, 55.5, 52.0, 43.4, 39.8, 33.9, 27.6, 22.8, 22.7. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3275, 2955, 2925, 2853, 2812, 1608, 1577, 1511, 1464, 1298, 1251, 1175, 1118, 1034, 1002, 971, 879, 827. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{31}N_2O_2$ 331.2390, found 331.2380.

*4-((R,E)-1-((2R,3S)-3-Isobutylaziridin-2-yl)-3-(p-tolyl)allyl)-morpholine (**8i**).* Scale: 0.050 g dimer (0.196 mmol). Yield: 0.072 g, 58%, yellow solid. R_f (1:9 MeOH/EtOAc): 0.32. ^{1}H NMR (399 MHz, $CDCl_3$) δ: 7.29−7.25 (m, 2H), 7.13 (d, J = 7.9 Hz, 2H), 6.44 (d, J = 15.9 Hz, 1H), 6.13 (dd, J = 15.9, 8.9 Hz, 1H), 3.74 (t, J = 4.7 Hz, 4H), 2.77−2.58 (m, 4H), 2.34 (s, 3H), 2.30 (t, J = 8.3 Hz, 1H), 1.86 (dd, J = 7.7, 3.1 Hz, 1H), 1.75−1.64 (m, 2H), 1.35 (dt, J = 13.2, 6.6 Hz, 1H), 1.23 (dt, J = 13.6, 6.6 Hz, 1H), 0.89 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.8, 133.9, 133.2, 129.4, 126.8, 126.4, 73.9, 67.2, 52.0, 43.4, 39.7, 33.9, 27.5, 22.7, 22.7, 21.3. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3273, 3022, 2955, 2923, 2900, 1514, 1448, 1436, 1288, 1268, 1118, 1002, 971. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{31}N_2O$ 315.2436, found 315.2436.

*4-((S)-Benzofuran-2-yl((2R,3S)-3-isobutylaziridin-2-yl)methyl)-morpholine (**8j**).* Scale: 0.051 g dimer (0.2 mmol). Yield: 0.0893, 71%, white solid. R_f (1:9 MeOH/EtOAc): 0.43. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55−7.46 (m, 2H), 7.29−7.19 (m, 2H), 6.59 (d, J = 0.9 Hz, 1H), 3.75 (t, J = 4.7 Hz, 4H), 2.96 (d, J = 8.1 Hz, 1H), 2.79−2.68 (m, 2H), 2.62−2.53 (m, 2H), 2.21 (dd, J = 8.1, 3.0 Hz, 1H), 1.76 (td, J = 6.3, 3.0 Hz, 1H), 1.56 (nonet, J = 6.7 Hz, 1H), 1.31 (dt, J = 13.3, 6.6 Hz, 1H), 1.21 (ddd, J = 13.6, 6.9, 6.3 Hz, 1H), 0.73 (d, J = 6.6 Hz, 3H), 0.72 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.7, 155.1, 128.0, 124.2, 122.9, 120.9, 105.2, 68.9, 67.1, 51.9, 43.4, 38.4, 34.2, 27.5, 22.5, 22.4. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3278, 2956, 2910, 2900, 2867, 1585, 1454, 1270, 1254, 1170, 1117, 1070, 1004, 886, 870, 812, 742. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{27}N_2O_2$ 315.2057, found 315.2067.

*4-((R)-1-((2R,3S)-3-Isobutylaziridin-2-yl)-3-phenylprop-2-yn-1-yl)-morpholine **8k**(syn) and 4-((R)-1-((2R,3S)-3-isobutylaziridin-2-yl)-3-phenylprop-2-yn-1-yl)morpholine **8k′**(anti).* Scale: 0.050 g dimer (0.2 mmol). Combined yield: 36%; **8k** 0.022 g, pale yellow solid; **8k′** 0.019 g, pale yellow gel. Diastereomeric ratio (by crude NMR integrations): **8k**:**8k′** 63:37. R_f (1:9 MeOH:EtOAc): **8k:** 0.16, **8k′**: 0.50. **8k**. ^{1}H NMR (399 MHz, $CDCl_3$) δ: 7.49−7.38 (m, 2H), 7.35−7.29 (m, 3H), 3.78 (dt, J = 5.8, 3.6 Hz, 4H), 3.58 (d, J = 5.9 Hz, 1H), 2.82 (ddd, J = 11.2, 5.5, 3.6 Hz, 2H), 2.66 (ddd, J = 11.2, 5.5, 3.6 Hz, 2H), 2.05 (td, J = 6.3, 2.7 Hz, 1H), 1.99 (dd, J = 5.7, 2.8 Hz, 1H), 1.81 (nonet, J = 6.7 Hz, 1H), 1.35 (td, J = 6.8, 3.9 Hz, 2H), 0.99 (d, J = 6.7 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 131.8, 128.4, 128.3, 122.5, 87.7, 82.9, 67.0, 61.5, 50.3, 42.7, 37.6, 34.2, 27.3, 22.8, 22.6. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3271, 2956, 2927, 2898, 2823, 1598, 1490, 1464, 1451, 1385, 1368, 1322, 1308, 1287, 1118, 1071, 861, 757, 692. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{27}N_2O$ 299.2123, found 299.2129. **8k′**. Coelutes with inseparable yellow impurity. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.47−7.39 (m, 2H), 7.36−7.29 (m, 2H), 4.06 (d, J = 2.7 Hz, 1H), 3.77 (dt, J = 6.0, 3.2 Hz, 4H), 2.83 (dt, J = 11.3, 4.3 Hz, 2H), 2.61 (dt, J = 11.3, 4.3 Hz, 2H), 2.04−1.88 (m, 2H), 1.76 (nonet, J = 6.6 Hz, 1H), 1.43 (dt, J = 13.8, 6.2 Hz, 1H), 1.24 (dt, J = 13.8, 6.2 Hz, 1H), 0.97 (d, J = 6.6 Hz, 6H). IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3278, 2956, 2927, 2868, 1601, 1490, 1464, 1453,1385, 1368, 1318, 1288, 1252, 1118, 1071, 1004, 894, 863, 757, 692. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{27}N_2O$ 299.2118, found 299.2118.

Preparation of Trimethyl((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethynyl)silane and TMS Cleavage of Products. Trimethylsilyl ethynyl boronic acid pinacol ester was prepared under Schlenk conditions using literature procedures:[30] Ethynyl trimethylsilane (2.0 mL, 14.15 mmol) was dissolved in dry diethyl ether (14 mL) and cooled to −78 °C. *n*-BuLi (5.44 mL, 2.6M) was added to the solution over 15 min and allowed to stir at −78 °C for 1 h to allow for complete metalation. In a second Schlenk flask, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.89 mL, 14.15 mmol) was dissolved in dry diethyl ether (14 mL) and cooled to −78 °C. The solution of lithiated alkyne was slowly added to the second flask by cannula over 15 min. The reaction produces a precipitate, which may halt stirring. Vigorous swirling of the flask may be required to commence stirring. After the mixture was stirred for 2 h at −78 °C, HCl in dioxane or ether (3.8 mL, 4.0 M) was added dropwise over 10 min, and the solution was warmed to room temperature and stirred for 20 min. The solution was filtered, and the solid LiCl was washed with ether. The filtrate was concentrated to yield a sticky yellowish solid that could be recrystallized multiple times with ethyl acetate/hexanes to yield a crystalline colorless solid.

After the PBM reaction was allowed to continue for 18 h, the same general workup procedure applied. TMS hydrolysis partially occurred with basic workup, but to fully deprotect, the crude stirred in 0.1 M NaOH in methanol for 2 h was used to generate **8l** and **8l′**.[31] Water was added and the methanol evaporated. The crude product was extracted with ethyl acetate three times, washed with brine, and dried over sodium sulfate. Compound **8l-TMS-alkyne** was never purified and characterized.

*4-((R)-1-((2R,3S)-3-Isobutylaziridin-2-yl)prop-2-yn-1-yl)-morpholine **8l** (syn) and 4-((S)-1-((2R,3S)-3-Isobutylaziridin-2-yl)-prop-2-yn-1-yl)morpholine **8l′**(anti).* Scale: 0.509 g dimer (0.2 mmol). Combined yield: 38%, **8l**: 0.041 g white solid, **8l′**: 0.096 g yellowish oil. R_f (1:9 MeOH/EtOAc): **8l-TMS-alkyne** = 0.52; **8l′-TMS-alkyne** = 0.65. R_f (1:9 MeOH/EtOAc): **8l** = 0.33; **8l′** = 0.52. Diastereomeric ratio (by crude NMR): **8l**:**8l′** 1:0.1. **8l**. ^{1}H NMR (399 MHz, $CDCl_3$) δ: 3.83−3.64 (m, 4H), 3.44 (dd, J = 5.5, 2.3 Hz, 1H), 2.85−2.65 (m, 2H), 2.65−2.51 (m, 2H), 2.35 (d, J = 2.3 Hz, 1H), 2.04−1.97 (m, 1H), 1.91 (dd, J = 5.5, 2.9 Hz, 1H), 1.79 (dqq, J = 13.4, 6.8, 6.8 Hz, 1H), 1.37 (ddd, J = 13.9, 7.0, 5.4 Hz, 1H), 1.26 (dt, J = 13.9, 7.0 Hz, 1H), 0.97 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 77.4, 75.6, 67.1, 60.8, 50.2, 42.9, 37.2, 34.2, 27.5, 23.0, 22.8. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3280, 3247, 2956, 2914, 2868, 2103, 1464, 1454, 1385, 1368, 1324, 1288, 1255, 1118, 1072, 1006, 862. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{13}H_{23}N_2O$ 223.1814, found 223.1804. **8l′**. ^{1}H NMR (399 MHz, $CDCl_3$) δ: 3.81 (br s, 1H), 3.78−3.65 (m, 4H), 2.79−2.70 (m, 2H), 2.58−2.47 (m, 2H), 2.34 (d, J = 2.3 Hz, 1H), 1.89 (t, J = 3.0 Hz, 1H), 1.85 (td, J = 6.3, 3.2 Hz, 1H), 1.82−1.68 (m, 2H), 1.36 (dt, J = 13.8, 6.3 Hz, 1H), 1.23 (ddd, J = 13.7, 7.5,

6.0 Hz, 2H), 0.95 (d, J = 6.7, 3H), 0.94 (d, J = 6.7, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 77.4, 76.2, 67.1, 60.1, 50.1, 42.4, 37.8, 31.7, 27.5, 23.0, 22.6. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3276, 2955, 2928, 2871, 2856, 2763, 2098, 1448, 1387, 1368, 1318, 1308, 1289, 1253, 1159, 1118, 1072, 1004, 864. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{13}H_{23}N_2O$ 223.1806, found 223.1805.

General Procedure for Thiobenzoic Acid Ring-Opening. Aziridine amine **8** (0.1 mmol) was dissolved in chloroform (1 mL, 0.1 M). The solution was stirred vigorously while thiobenzoic acid (0.5 mmol) was added by syringe, and the yellow solution was stirred for 10 h. Reaction progress could be observed by TLC if a mini-work up was performed by mixing an aliquot of the reaction with a saturated sodium bicarbonate solution. The reaction was also be monitored by LC/MS. Longer stirring allowed for full conversion of mono-benzoylated product to the bis-benzoylated product. Products were purified via silica gel chromatography neutralized with 1% triethylamine and an eluent system generally of gradient hexanes to 40% ethyl acetate in hexanes. The thioester was quite labile and could decompose over time.

*S-((3S,4S,5R,E)-5-Benzamido-3-morpholino-1,7-diphenylhept-1-en-4-yl) Benzothioate (**11a**).* Scale: 0.1 mmol. Yield: 0.0304 g, 52%, white solid. R_f (3:2 hexanes/ethyl acetate): 0.53. ^{1}H NMR (399 MHz, $CDCl_3$) δ: 7.90−7.82 (m, 2H), 7.71−7.67 (m, 2H), 7.55−7.44 (m, 2H), 7.41 −7.34 (m, 4H), 7.33−7.10 (m, 10H), 6.43 (d, J = 15.7 Hz, 1H), 6.37 (br d, J = 9.4 Hz, 1H), 6.07 (dd, J = 15.8, 9.5 Hz, 1H), 5.15−5.02 (m, 1H), 4.58 (dd, J = 10.6, 3.5 Hz, 1H), 3.61 (t, J = 4.7 Hz, 4H), 3.18 (t, J = 10.0 Hz, 1H), 2.95−2.86 (m, 2H), 2.86−2.68 (m, 2H), 2.41 (dt, J = 11.2, 4.6 Hz, 2H), 2.07 (dtd, J = 13.7, 8.2, 2.8 Hz, 1H), 1.84 (dddd, J = 13.6, 10.9, 7.8, 5.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.3, 167.6, 141.6, 136.9, 136.5, 135.5, 134.9, 133.7, 131.5, 128.8, 128.8, 128.7, 128.7, 128.7, 128.6, 127.8, 127.5, 127.0, 126.6, 126.2, 124.8, 69.3, 67.3, 49.9, 48.8, 33.0, 32.7. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3323, 3082, 3059, 3024, 2955, 2850, 2825, 1662, 1652, 1645, 1602, 1580, 1489, 1448, 1207, 1176, 1158, 1115, 1071, 907. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{37}H_{39}N_2O_3S$ 591.2665, found 591.2675.

*S-((3R,4R,5S,E)-5-Benzamido-7-methyl-3-morpholino-1-phenyloct-1-en-4-yl) Benzothioate (**11b**).* Scale: 0.1 mmol. Yield: 0.033 g, 61%, white solid. R_f (3:2 hexanes/ethyl acetate): 0.53. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94−7.79 (m, 2H), 7.77−7.64 (m, 2H), 7.54−7.48 (m, 1H), 7.47−7.42 (m, 1H), 7.40−7.33 (m, 4H), 7.31−7.21 (m, 4H), 7.21−7.14 (m, 1H), 6.46 (d, J = 15.8 Hz, 1H), 6.17 (br d, J = 9.4 Hz, 1H), 6.11 (dd, J = 15.8, 9.5 Hz, 1H), 5.23 (ddt, J = 10.1, 9.0, 3.6 Hz, 1H), 4.60 (dd, J = 11.1, 3.2 Hz, 1H), 3.86−3.76 (m, 4H), 3.22 (dd, J = 11.0, 9.5 Hz, 1H), 3.02 (dd, J = 10.1, 5.3 Hz, 2H), 2.52 (dt, J = 10.7, 4.5 Hz, 2H), 1.85−1.70 (m, 1H), 1.54−1.42 (m, 2H), 1.06 (d, J = 6.4 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.2, 167.5, 136.9, 136.6, 135.5, 133.6, 131.4, 128.7, 128.6, 128.6, 127.8, 127.5, 127.0, 126.6, 124.9, 69.3, 67.5, 50.2, 47.1, 40.1, 25.2, 24.1, 22.0. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3416, 3081, 3059, 3027, 2957, 2929, 2894, 2854, 1661, 1640, 1603, 1325, 1251, 1207, 1176, 1115, 1072, 906. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{33}H_{38}N_2O_3S$ 543.2695, found 543.2675.

*S-((4R,5S,6R,E)-5-Benzamido-2-methyl-6-morpholino-8-phenyloct-7-en-4-yl) Benzothioate (**12b**).* Scale: 0.07 mmol−TFE as solvent. Yield: 0.0126 g, 36%, yellow gel. R_f (3:2 hexanes/ethyl acetate): 0.66. ^{1}H NMR (399 MHz, $CDCl_3$) δ: 7.98−7.93 (m, 2H), 7.84−7.79 (m, 2H), 7.57−7.21 (m, 11H), 6.64 (br d, J = 7.8 Hz, 1H), 6.59 (d, J = 15.8 Hz, 1H), 6.31 (dd, J = 15.8, 9.6 Hz, 1H), 4.72 (ddd, J = 10.2, 7.9, 2.4 Hz, 1H), 4.36 (ddd, J = 10.7, 4.3, 2.3 Hz, 1H), 3.73−3.49 (m, 4H), 3.24 (t, J = 9.9 Hz, 1H), 2.81 (t, J = 4.6 Hz, 1H), 2.76 (ddd, J = 9.7, 6.4, 3.2 Hz, 2H), 2.53−2.40 (m, 2H), 1.87−1.71 (m, 1H), 1.66−1.51 (m, 2H), 0.95 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H). Impurity present in NMR; see the Supporting Information for ^{13}C NMR.

*S-((2R,3S,E)-2-Benzamido-3-morpholino-5-phenylpent-4-en-1-yl) Benzothioate (**12c**).* Scale: 0.08 mmol. Yield: 0.0191 g, 48%, white solid. R_f (3:2 hexanes/ethyl acetate): 0.26. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.98−7.88 (m, 2H), 7.78−7.73 (m, 2H), 7.59−7.27 (m, 13H), 6.80 (br d, J = 6.9 Hz, 1H), 6.61 (d, J = 15.9 Hz, 1H), 6.21 (dd, J = 15.9, 9.5 Hz, 1H), 4.64 (qd, J = 7.6, 3.8 Hz, 1H), 3.78 (dd, J = 14.1, 3.8 Hz, 1H), 3.74−3.64 (m, 4H), 3.38 (dd, J = 14.2, 7.7 Hz, 1H), 3.23 (t, J = 8.7 Hz, 1H), 2.70 (dt, J = 9.8, 4.1 Hz, 2H), 2.64−2.52 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 192.2, 167.5, 136.9, 136.9, 136.3, 134.4, 133.7, 131.7, 128.9, 128.7, 128.3, 127.5, 127.1, 126.8, 126.7, 124.3, 70.2, 67.4, 50.6, 50.2, 30.2. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3322, 3081, 3059, 3027, 3000, 2958, 2925, 2893, 2854, 2819, 1713, 1652, 1633, 1616,, 1580, 1576, 1549, 1516, 1486, 1207, 1116, 913. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{29}H_{31}N_2O_3S$ 487.2047, found 487.2049.

*S-((3R,4R,5S,E)-5-Benzamido-7-methyl-1-phenyl-3-(pyrrolidin-1-yl)oct-1-en-4-yl) Benzothioate (**11d**).* Scale: 0.1 mmol. Yield: 0.036 g, 48%, pale yellow solid. R_f (3:2 hexanes/ethyl acetate): 0.52. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.97−7.91 (m, 2H), 7.71 (br d, J = 7.3 Hz, 2H), 7.57−7.50 (m, 1H), 7.47−7.20 (m, 10H), 6.67 (br s, 1H), 6.60 (d, J = 15.9 Hz, 1H), 6.24 (dd, J = 15.8, 9.4 Hz, 1H), 4.94 (tt, J = 10.0, 3.9 Hz, 1H), 4.51 (dd, J = 7.6, 4.0 Hz, 1H), 3.49 (dd, J = 10.4, 6.8 Hz, 1H), 2.86−2.76 (m, 2H), 2.71−2.61 (m, 2H), 1.84−1.67 (m, 5H), 1.59−1.45 (m, 2H), 0.96 (d, J = 6.5 Hz, 3H), 0.93 (d, J = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 191.2, 167.0, 137.0, 136.6, 134.8, 133.6, 131.4, 128.8, 128.7, 128.6, 128.6, 127.9, 127.6, 127.1, 126.7, 66.7, 52.0, 49.9, 49.2, 42.0, 25.3, 23.8, 23.5, 21.8. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3428, 3312, 3081, 3059, 3027, 2958, 2871, 2807, 1660, 1652, 1598, 1368, 1207. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{33}H_{39}N_2O_2S$ 527.2732, found 527.2727.

*S-((3R,4R,5S,E)-5-Benzamido-3-(diallylamino)-7-methyl-1-phenyloct-1-en-4-yl) Benzothioate (**11f**).* Scale: 0.1 mmol. Yield: 77%, pale yellow oil. R_f (3:2 hexanes/ethyl acetate): 0.78. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87−7.81 (m, 2H), 7.71−7.63 (m, 2H), 7.54−7.14 (m, 11H), 6.39 (d, J = 15.7 Hz, 1H), 6.12 (br d, J = 9.4 Hz, 1H), 6.02 (dd, J = 15.8, 9.7 Hz, 1H), 6.03−5.92 (m, 2H), 5.32−5.09 (m, 5H), 4.60 (dd, J = 11.3, 3.0 Hz, 1H), 3.67 (ddt, J = 13.8, 4.0, 1.9 Hz, 2H), 3.49 (dd, J = 11.3, 9.6 Hz, 1H), 2.90 (dd, J = 13.8, 8.8 Hz, 2H), 1.81−1.70 (m, 1H), 1.51 (ddd, J = 13.0, 10.0, 2.9 Hz, 1H), 1.41 (ddd, J = 13.6, 11.3, 4.0 Hz, 1H), 1.05 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.3, 167.2, 137.1, 137.0, 136.9, 135.4, 135.2, 133.5, 131.3, 128.7, 128.6, 128.6, 127.6, 127.5, 127.1, 126.6, 124.7, 117.8, 63.2, 53.0, 51.3, 46.9, 39.5, 25.3, 24.2, 21.9. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3308, 3060, 3029, 2956, 2868, 1721, 1699, 1652, 1635, 1533, 1516, 1486, 1448, 1250, 1207, 1116, 907. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{35}H_{41}N_2O_2S$ 553.2887, found 553.2883.

General Procedure for *p*-Nitrobenzoic Acid Ring-Opening. Diamine **8** (0.1 mmol) and *p*-nitrobenzoic acid (0.12 mmol) were combined in a 2-dram screw cap vial and dissolved in DMF (1.0 mL, 0.1 M). Triethylamine (0.01 mmol) was added via syringe and the vessel sealed and stirred in an oil bath at 65 °C for 24 h. The solvent of the yellow solution was removed in vacuo, redissolved in ethyl acetate, washed with saturated sodium bicarbonate solution and brine, and dried over sodium sulfate. The products were purified by silica gel column chromatography generally with gradient hexanes to 30% acetone in hexanes and coleutes with the minor diastereomer as well as an unknown impurity only furnished through column purification. The reported yields are of ∼95% purity.

*N-((3R,4R,5R,E)-5-Hydroxy-4-morpholino-1,7-diphenylhept-6-en-3-yl)-4-nitrobenzamide (**13a**).* Scale: 0.1 mmol. Yield: 0.0191 g, 37%, yellow oil. R_f (1:1 hexanes/acetone): 0.39. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.23−8.17 (m, 2H), 7.81−7.71 (m, 2H), 7.35−7.13 (m, 10H), 6.78 (d, J = 9.1 Hz, 1H), 6.61 (dd, J = 15.9, 1.1 Hz, 1H), 6.26 (dd, J = 15.9, 7.0 Hz, 1H), 4.57 (tdd, J = 9.3, 5.5, 4.0 Hz, 1H), 4.48 (ddd, J = 7.1, 6.0, 1.2 Hz, 1H), 3.66 (t, J = 4.6 Hz, 4H), 2.86−2.78 (m, 4H), 2.76−2.70 (m, 2H), 2.68 (t, J = 5.7 Hz, 1H), 2.16−2.09 (m, 1H), 2.06−1.98 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 164.8, 149.7, 141.3, 139.6, 136.2, 132.3, 130.0, 128.8, 128.8, 128.5, 128.3, 128.1, 126.6, 126.3, 123.9, 71.1, 71.0, 67.8, 51.00, 49.3, 35.8, 32.7. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3385, 3106, 3083, 3026, 2959, 2854, 1648, 1643, 1601, 1525, 1496, 1452, 1346, 1297, 1153, 1116, 911. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{30}H_{34}N_3O_5$ 516.2489, found 516.2493.

*N-((4S,5S,6S,E)-6-Hydroxy-2-methyl-5-morpholino-8-phenyloct-7-en-4-yl)-4-nitrobenzamide (**13b**).* Scale: 0.1 mmol. Yield: 0.0234 g, 50% pale yellow solid. R_f (1:1 hexanes/acetone): 0.37. ^{1}H NMR (500

MHz, $CDCl_3$) δ: 8.24−8.19 (m, 2H), 7.91−7.85 (m, 2H), 7.35−7.23 (m, 5H), 6.77 (d, J = 9.3 Hz, 1H), 6.64 (d, J = 15.9 1H), 6.29 (dd, J = 15.9, 7.3 Hz, 1H), 4.60 (tt, J = 9.2, 5.2 Hz, 1H), 4.49 (ddd, J = 7.4, 6.5, 1.1 Hz, 1H), 3.75−3.64 (m, 4H), 2.95−2.81 (m, 4H), 2.63 (dd, J = 6.6, 4.8 Hz, 1H), 1.70−1.59 (m, 1H), 1.59−1.53 (m, 2H), 0.96 (d, J = 6.4 Hz, 3H), 0.95 (d, J = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 164.6, 149.7, 139.8, 136.2, 132.4, 130.2, 128.8, 128.1, 126.6, 123.9, 71.6, 71.1, 67.8, 51.1, 47.5, 43.9, 25.2, 23.6, 22.0. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3333, 2958, 2934, 2868, 2854, 1654, 1645, 1601, 1524, 1487, 1449, 1346, 1117. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{26}H_{34}N_3O_5$ 468.2487, found 468.2493.

*N-((4S,5S,6S,E)-6-Hydroxy-2-methyl-8-phenyl-5-(pyrrolidin-1-yl)-oct-7-en-4-yl)-4-nitrobenzamide (**13d**).* Scale: 0.1 mmol. Yield: 0.0359 g, 80%, yellow solid. R_f (7:3 hexanes/acetone): 0.28. Mp: 99−110 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.29−8.24 (m, 2H), 7.95 (br d, J = 8.6 Hz, 2H), 7.41−7.23 (m, 5H), 6.70 (dd, J = 15.9, 1.2 Hz, 1H), 6.30 (dd, J = 15.9, 5.3 Hz, 1H), 4.67−4.56 (m, 2H), 4.37 (br s, 1H), 2.92−2.80 (br s, 2H), 2.76−2.63 (s, 3H), 1.86−1.61 (m, 6H), 1.51−1.42 (m, 1H), 1.02 (br d, J = 6.4 Hz, 3H), 1.00 (d, J = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 164.4, 149.7, 140.0, 136.6, 132.5, 130.5, 128.8, 128.2, 128.0, 126.6, 123.9, 69.7, 68.2, 51.9, 49.5, 44.0, 25.4, 23.7, 23.0, 22.8. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3308, 3196, 3081, 3054, 3028, 2958, 2871, 1682, 1652, 1635, 1600, 1340, 1300, 1265, 1152, 1108, 1071, 1015, 968, 870, 842. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{26}H_{34}N_3O_4$ 452.2535, found 452.2544.

General Procedure for Raney Nickel Reduction. In a 2-dram vial, unpurified **11a**/**b** was dissolved in methanol (1.0 mL), and Raney nickel suspension (1.0 mL) was added. The solution bubbled and was sealed and vigorously stirred at room temperature overnight. The slurry was filtered through a plug of Celite and the solvent removed in vacuo. The crude products were purified by silica gel chromatography. The purified products turned red over time.

*N-((3R,5S)-5-Morpholino-1,7-diphenylheptan-3-yl)benzamide (**14a**).* Scale: 0.1 mmol of **8a**. Yield: 0.0186 g, 46% (two steps), pale yellow oil−turns deep red upon storage. R_f (3:2 hexanes/ethyl acetate): 0.78. ^{1}H NMR (399 MHz, $CDCl_3$) δ: 7.71 (d, J = 7.1 Hz, 2H), 7.52−7.46 (m, 1H), 7.45−7.39 (m, 2H), 7.33−7.11 (m, 11H), 4.26−4.14 (m, 1H), 3.64−3.49 (m, 4H), 2.69−2.48 (m, 4H), 2.48−2.39 (m, 1H), 2.38−2.29 (m, 2H), 2.04−1.85 (m, 3H), 1.81−1.69 (m, 2H), 1.65−1.46 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.8, 142.0, 141.9, 135.2, 131.5, 128.6, 128.6, 128.6, 128.5, 127.1, 126.1, 126.0, 67.4, 62.1, 49.9, 48.4, 36.9, 33.8, 33.5, 32.3, 30.4. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3282, 3061, 3027, 2954, 2929, 2867, 1656, 1637, 1602, 1576, 1539, 1490, 1454. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{30}H_{37}N_2O_2$ 457.2850, found 457.2855.

*N-((4S,6R)-2-Methyl-6-morpholino-8-phenyloctan-4-yl)-benzamide (**14b**).* Scale: 0.1 mmol of **8b**. Yield: 0.0210 g, 47% (two steps), pale yellow gel−turns deep red upon storage. R_f (3:2 hexanes/ethyl acetate): 0.78. ^{1}H NMR (399 MHz, $CDCl_3$) δ: 7.79−7.71 (m, 2H), 7.52−7.46 (m, 1H), 7.43 (ddt, J = 8.4, 6.6, 1.5 Hz, 2H), 7.28−7.22 (m, 2H), 7.20−7.12 (m, 3H), 6.72 (d, J = 7.4 Hz, 1H), 4.40−4.17 (m, 1H), 3.70−3.54 (m, 4H), 2.73−2.52 (m, 4H), 2.52−2.43 (m, 1H), 2.42−2.34 (m, 2H), 1.96−1.81 (m, 1H), 1.79−1.65 (m, 2H), 1.65−1.47 (m, 3H), 1.35 (ddd, J = 13.7, 8.0, 5.5 Hz, 1H), 0.97 (d, J = 1.9 Hz, 3H), 0.96 (d, J = 2.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.3, 142.0, 135.1, 131.3, 128.5, 128.4, 128.3, 126.9, 125.8, 67.4, 61.5, 48.3, 47.6, 45.0, 34.7, 33.4, 30.5, 25.1, 23.0, 22.6. IR (KBr, thin film) $\tilde{\nu}$ (cm^{-1}): 3299, 3061, 3026, 2927, 2857, 1656, 1635, 1576. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{26}H_{37}N_2O_2$ 409.2844, found 409.2855.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra, X-ray crystallography data, and CIF. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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